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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,860	09/12/2003	Gregory P. Pogue	LSBC-POGUE-A1A	7908
27860 7590 02/23/2007 LARGE SCALE BIOLOGY CORPORATION 3333 VACA VALLEY PARKWAY SUITE 1000 VACAVILLE, CA 95688			EXAMINER LONG, SCOTT	
			ART UNIT	PAPER NUMBER
			1633	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/23/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/660,860	Applicant(s) POGUE ET AL.	
	Examiner Scott D. Long	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 5-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 5-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Detailed Action

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Claims 1-2 and 5-10 are newly amended. Claims 3-4 are withdrawn. Claims 1-2 and 5-10 are under examination.

Priority

This application claims benefit from provisional U.S. Application No. 60/410,879, filed 13 September 2002. The instant application has been granted the benefit date, 13 September 2002, from the application 60/410,879.

Response to Arguments

Claim Objections

The objections to claims 1 and 9 are withdrawn in response to Applicant's amendment or arguments. The claim language objected to in the previous action have been deleted and/or amended.

35 USC 112

The rejection under paragraph 2 of claims 1-2, 5, and 8 as being indefinite, is withdrawn in response to Applicant's amendment or arguments.

The rejection under paragraph 1 of claims 1-2, 5-10 as failing to comply with the written description requirement, is maintained. Applicant's arguments filed 8 January 2007 have been fully considered but they are not persuasive. The claim amendments now limit the invention to gene silencing in plant hosts. Therefore the examiner's rejections based on lack of written description for gene silencing in animal hosts, using alphavirus and rubivirus are moot. However, the examiner continues to assert the inventor was not in possession of vectors for silencing the enormous number of genes encompassed within the scope of the claims within the enormous number of plant hosts encompassed by the claims. Additionally, the applicant fails to describe the structure of the hairpin sequences capable of silencing any given gene, beyond the general statement that there is an inverted repeat. The applicant also fails to particularly point out critical consensus regions or motifs of the genus of hairpin sequences.

Applicant's arguments in regard to the rejection under paragraph 1 of claims 1-2 and 5-10 for lack of enablement filed 8 January 2007 have been fully considered and have been found to be partially persuasive.

The rejection under paragraph 1 of claims 1 and 6-10 for lack of enablement is withdrawn in response to Applicant's amendment or arguments. The rejection under

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paragraph 1 of claims 2 and 5 as for lack of enablement is maintained. Particularly, the process of inhibiting cytoplasmic inhibition and method for determining gene function through a process of inhibiting cytoplasmic inhibition are not enabled. The breadth of the claims encompasses gene silencing for an enormous number of genes within a huge number of plant species. Guidance was provided for only two examples of gene silencing in plants.

The applicant's arguments are that (1) the exemplary plant viruses of the specification (i.e. – TMV and BSMV) are sufficient to demonstrate that any virus could be used to deliver hairpin RNA. While TMV and BSMV might be capable of delivering hairpin RNA to a large variety of monocotyledonous and dicotyledonous plants, a skilled artisan would not necessarily know how to deliver hairpin RNA from any RNA virus genome (as in claims 2 and 5). For example, could a lentivirus (e.g. – HIV) be used to deliver the hairpin to a plant host? The applicant also argues that (2) the exemplified hairpin structures for inhibiting GFP and PDS are sufficient to overcome any unpredictability in inhibiting other genes. The hairpin RNAs for GFP and PDS have distinct structures. It is not clear to the examiner how a hairpin RNA for one of these genes makes obvious the structure of the other. Furthermore, it is not clear from the specification which regions of the coding sequence of the target gene is most useful for designing hairpin sequences. How can an artisan know how to silence any particular gene, given only the limited teachings of the specification? Since the applicant is not in possession of a whole genus of hairpin RNAs for silencing a large number of genes, a skilled artisan would not know how to use a hairpin RNA to silence any given gene.

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Finally, Vance et al. (Science. 2001. Vol.292: 2277-2280) teach that some plants are "impaired in RNA silencing" (page 2280. col.1), making RNA hairpin gene silencing unpredictable.

35 USC 102

The rejection of claims 1 as anticipated over Symonds et al (US-5,712,384), is withdrawn in response to Applicant's amendment or arguments. In particular, the claim amendments have limited the invention to methods and vectors targeted to plant hosts. Symonds et al. does not teach their vectors and methods for silencing genes in plant hosts.

35 USC 103

The rejection of claims 1-2, 5, and 8-10 as unpatentable over Graham (US-6,573,099) in view of Kovacs et al. (US-7,034,141), is withdrawn in response to Applicant's amendment or arguments. The claim amendments have limited the invention to vectors and methods targeted to plant hosts. Kovacs et al. does not teach plant vectors.

Claims 1-2 and 5-8 remain rejected as unpatentable over Graham (US-6,573,099) in view of Scholthof et al. (Ann Rev Phytopath.. 1996: 34; 299-323) for the reasons of record.

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Applicant's arguments have been fully considered but are not persuasive.

Applicants traverse the instant rejection on the following grounds:

The applicant's position is that there is no motivation to combine the teachings of Graham and Scholthof et al. The applicant infers that Graham does not teach the delivery of palindromic sequences for gene silencing in plants, "Graham teaches something about making and using a palindrome within an animal virus, Scholthof et al., is a review of transient expression of foreign genes by plant virus gene vectors" (page 12, parag.1, Applicant's Response 1/8/2007). Furthermore, the applicant asserts that "there appears to be nothing in either reference that would motivate one skilled in the art to combine them...they do not appear to have any discussions in common....A person skilled in the animal virus art would not look to a reference that merely contains a list of plant viruses and declare that an intention than can be applied to the interaction between an animal virus and an animal host would also apply to plants and their viruses" (page 12, parag.2, Applicant's Response 1/8/2007). The applicant also asserts that the examiner used hindsight reasoning "to set up a ground of rejection." (page 12, Applicant's response).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

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reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Contrary to Applicant's assertions, Graham teaches "modifying endogenous gene expression in a cell, tissue or organ of a transgenic organism, in particular a transgenic animal or plant." (col.1, lines 8-10). Graham further teaches, "synthetic genes of the present invention may be introduced to a suitable cell, tissue or organ without modification as linear DNA in the form of a genetic construct, optionally contained within a suitable carrier, such as a cell, virus particle or liposome, amongst others." (col.13, lines 57-61). In addition to gene expression vectors specific to plants, Scholthof et al. describe gene silencing in plants "through...events that involve RNA degradation" (page 314, parag.2). Using specific plant viruses (tobacco mosaic virus or barley strip mosaic virus) for silencing genes in plants would be obvious considering the teachings of Graham in view of Scholthof et al.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claim 1-2 and 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What is a viral RNA-based expression vector? It is not clear what are the meets and bounds of this phrase? Clarification is required.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What is a viral RNA-based expression vector, derived from the viruses? What viruses are being referred to? Clarification is required.

Claims 1-2 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention

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is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement*; (Federal Register/Vol 66, No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 1-2 and 5-10 are newly amended to recite a "viral RNA-based expression vector." This phrase is not defined within the specification. Does it mean RNA viruses, plasmids that comprise whole genomes of RNA viruses, plasmids that comprise portions of RNA viral genomes, or other types of vectors? An artisan would not understand that the applicant is in possession of every type of possible "viral RNA-based expression vector."

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66, No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH

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EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the phrase a "viral RNA-based expression vector" was not defined within the specification, and that it is not an art recognized term, there are a potentially large numbers possible meanings and vectors which might be encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5, and 8-10 are rejected under 35 U.S.C. 102b) as being anticipated by Wang et al. (Molecular Plant Pathology. 2000. 1;6: 347-356).

The instant invention is directed to a DNA construct encoding a genome of an infectious clone of a viral RNA-based expression vector, the genome comprising a hairpin, the hairpin being comprised of a first hairpin sequence fragment and a second hairpin sequence fragment: a) the first hairpin sequence fragment corresponding to a gene encoded within the nucleus of a target plant host, said hairpin sequence being a sequence fragment being greater than 10 bases in length and in the sense orientation; and b) the second hairpin sequence fragment following the first hairpin sequence derived from the first hairpin sequence fragment and in the reverse complement orientation; wherein if an intervening sequence is present, then the intervening sequence is of no greater length than the collective length of the two sequence fragments comprising the hairpin.

Wang et al. teach, "posttranscriptional gene silencing (PTGS) can be induced in plants using transgenes that encode double stranded (ds) or self-complementary 'hairpin' (hp) RNA...transformation of barley plants with a construct that encodes a

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hpRNA containing the polymerase gene sequences" (page 348, col.1). Wang et al. also teach, "degradation mechanism is likely to have many parallels with that of RNA interference (RNAi) in nematodes, flies, and fungi....In a cell free system in *Drosophila*, the RNAi-inducing RNA duplex has been elegantly shown to be cleaved into 21–23 bp dsRNA molecules in a nucleoprotein complex which then target single stranded RNA molecules of the same sequence for nucleolytic cleavage....The same mechanism probably operates in plants, because...small (25nt) RNA molecules are associated with virus resistance and PTGS in tobacco." (page 355). Wang et al. teaches the use of this type of gene silencing in both monocots (cereals) and dicots (potato).

Accordingly, Wang et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Molecular Plant Pathology. 2000. 1;6: 347-356) in view of Scholthof et al. (Annual Review of Phytopathology, September 1996, Vol. 34, Pages 299-323)

Claims 6-7 are directed to tobacco mosaic virus (TMV) and barley striped mosaic virus as vectors for expressing the invention of claim 1.

The teachings of Wang et al. are described above in the previous 102(b) section, which satisfy all the limitations of claim 1. Wang et al. do not teach the particular use of tobacco mosaic virus (TMV) or barley striped mosaic virus, as specified in claims 6-7.. While Wang et al. do not specifically teach using TMV or BSMV viruses for hairpin expression, they teach the use of *Agrobacterium* as a vector for the hairpin.

Scholthof et al teach tobacco mosaic virus (TMV) and barley striped mosaic virus (BSMV) as plant virus gene vectors for transient expression in plants. (p. 299, introduction and p.307). Scholthof et al. also teach *Agrobacterium* as vectors for introducing nucleic acids into plants (page 300). In addition to gene expression vectors specific to plants, Scholthof et al. describe gene silencing in plants "through...events that involve RNA degradation" (page 314, parag.2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Wang et al. and Scholthof et al. to generate vectors comprising specific RNA viruses (viruses tobacco mosaic virus, barley striped mosaic virus) as vectors for hairpin gene silencing sequences. Utilizing TMV and BSMV as vectors for the invention of Wang et al. as applied to plants, would have been obvious because these viruses are commonly used as expression vectors for plants.

The person of ordinary skill in the art would have been motivated to combine Scholthof et al. viruses with the Wang et al. invention because "plant virus gene vectors for expression of foreign genes in plants provides attractive biotechnological tools" (Scholthof et al. p.299 abstract). Wang et al. teach introduction of hairpin RNA into Barley plants for gene silencing and Scholthof et al teach RNA-based gene silencing and the use of appropriate plant virus vectors, TMV and BSMV. Therefore, a skilled artisan would be motivated to utilize vectors comprising TMV or BSMV to introduce gene silencers in to cereals. Furthermore, Scholthof et al. suggest that virus-based nucleic acid transfer in plants might be preferable to *Agrobacterium*-based gene transfer (Scholthof et al., pages 300-301).

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Wang et al. and Scholthof et al. because Wang et al. teach introduction of hairpin RNA into Barley plants for gene silencing and Scholthof et al teach RNA-based gene silencing and the use of appropriate plant virus vectors, TMV

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and BSMV. All of the technologies were well developed enough at the time of the instant application to assure success.

Therefore the method as taught Wang et al. in view of Scholthof et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**.

The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1633


JANET L. EPPS-FORD, PH.D.
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